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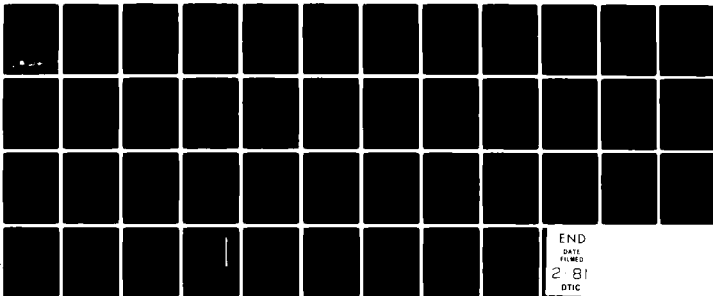
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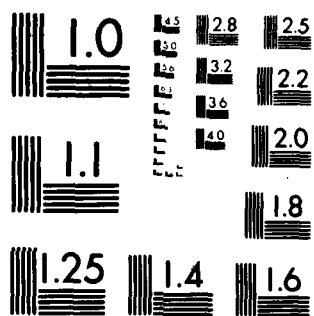
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INFLUENCE OF NUTRITIONAL FACTORS ON LIPID METABOLISM

E. WAYNE ASKEW, PhD, MAJ MS

DIVISION OF NUTRITION TECHNOLOGY

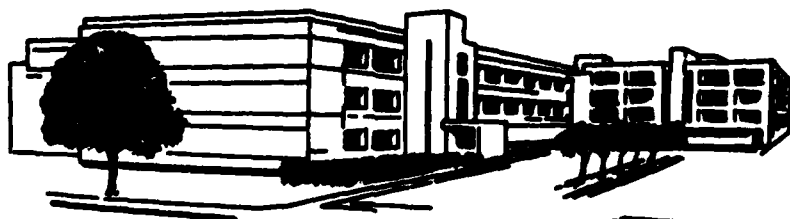
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Influence of Nutritional Factors on Lipid Metabolism--Askew

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ABSTRACT

Modification of the composition of the diet can cause alterations in the enzyme activities of different tissues and organs. Changes in enzyme activity in response to diet are part of the process of metabolic regulation enabling a biological system to function efficiently and harmoniously. Lipid metabolism is closely coordinated with the diet because lipids are repositories for excess energy and a source of energy during periods of deprivation. The effect of diet on lipid metabolism in the liver, muscle, and adipose tissue frequently differs and is species dependent. Fatty acid uptake, synthesis, esterification, mobilization, and oxidation are coordinated metabolic processes that are under dietary control.

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PREFACE

This review was originally written to comprise a chapter in a handbook series on nutrition. Internal problems at the publishing company precluded timely publication of the volume for which this review was solicited. The author decided to publish the material as an Institute Report before the information it contained became outdated.

ACKNOWLEDGEMENTS

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It is well substantiated that modification of the composition of the diet by increasing or decreasing its constituents can cause alterations in the enzyme activities of different tissues and organs (1). Changes in enzyme activity in response to diet are part of the process of metabolic regulation enabling a biological system to function efficiently and harmoniously. One of the most responsive metabolic pathways to diet is the sequence of reactions involved in lipid synthesis and degradation. Lipid metabolism must be closely coordinated with the diet because lipids, by their very nature, are repositories for excess energy and a source of energy during periods of deprivation. The ability of higher organisms to store excess dietary carbohydrate in the form of carbohydrates is essentially limited to that quantity that can be deposited in the liver and muscle. This quantity of energy is extremely limited (approximately 1000 kcal) compared to the quantity of energy that can be stored as lipid (approximately 141,000 kcal) in the adult man (2). Dietary carbohydrates in excess of energy requirements are converted to fat for storage and subsequently utilized as fat; net synthesis of carbohydrate from fat can not occur because of net carbon considerations (3). In addition to the central role of lipid metabolism in energy metabolism, consideration must be given to the specific type of carbohydrate composing the diet in assessing the influence of diet on lipid metabolism. Certain sugars influence lipogenesis to a greater or lesser degree than would be predicted based upon their caloric content (4). The accretion of fat is dependent not only upon the rate of delivery of energy to the adipose tissue and liver but also upon the chemical nature of these precursors. This review of the influence of diet on lipid metabolism will illustrate through selective examples the manner in which lipid metabolism responds to the quantity and composition of the diet. The scientific literature is replete with several excellent reviews concerning the effect of diet on specific processes or pathways of lipid metabolism (5-13). The reader is referred to these reviews for a more focused and comprehensive review of specific areas of lipid metabolism. Because this review attempts to cover lipid metabolism in general, the examples and references are by no means complete, but merely illustrative. The topic of the effect of diet on blood lipids alone is so extensive that it is beyond the scope of this review. This review will encompass the effect of diet on lipid metabolism in the liver, muscle, and adipose tissue, with emphasis on fatty acid uptake, synthesis, esterification, mobilization, and oxidation.

Interpretation of Dietary Effects

Prior to generalizing some of the major effects of diet on lipid metabolism, it is important to recognize that the literature on this topic is in many cases confusing and even contradictory. A number of

factors can be suggested to account partially for these experimental contradictions: 1) species differences, 2) organ differences, 3) level of dietary fat, carbohydrate or protein fed, 4) duration of the feeding experiment and 5) time relationships between food intake and the enzyme response being investigated.

For example, in the case of lipogenesis, the relative importance of the two major organs of lipogenesis, liver and adipose tissue, varies with the species (11). Birds and humans are similar but different from the rat, and other mammals seem to vary between these two extremes (14). Although the most commonly utilized experimental animal is the rat, it appears to be less than an ideal experimental model to study the regulation of lipogenesis for humans (14). Both the liver and adipose tissue in the rat contribute significantly to lipogenesis with the adipose organ predominating under most dietary circumstances, whereas in man adipose tissue is of minor importance to total lipogenesis. In addition to species-specific responses, organ-specific responses to dietary factors must be considered. For example, dietary fructose increased lipogenesis in rat liver but decreased lipogenesis in rat adipose tissue (15). Dietary butanediol did not influence rat adipose tissue lipogenesis but decreased hepatic lipogenesis (16). Safflower oil compared to lard as a dietary fat source decreased hepatic fatty acid synthesis but increased adipose tissue fatty acid synthesis in the rat but had little effect on fatty acid synthesis in either organ in the chick (17).

Another difficulty in interpreting studies where the proportion of calories coming from carbohydrate, fat or protein as one of the experimental variables is that it is impossible to vary one of these three dietary components without varying at least one other. Ascribing a particular effect to the abundance or lack of abundance of one component becomes one of semantics, i.e., a high carbohydrate diet is also a low fat diet if protein is held constant (8,18). Is the observed effect due to the presence of carbohydrate or to the lack of fat? Yet another factor in interpreting the effect of diet on lipid metabolism is the level of protein in the diet. Increased fat deposition such as that seen following fasting and refeeding in the rat is dependent upon the presence of dietary protein (8). The activity of glucose-6-phosphate dehydrogenase following fasting and refeeding in the rat is especially dependent upon the presence of adequate dietary protein (8,11). Not all of the enzymes associated with lipogenesis, however, are as dependent upon dietary protein as the pentose shunt enzymes. Malic enzyme seems to contrast to glucose-6-phosphate dehydrogenase with respect to the protein content of the diet. Feeding a nitrogen-free diet to fasted rats increased hepatic malic enzyme activity, but not glucose-6-phosphate dehydrogenase activity (19-21). Tepperman and Tepperman (7) have suggested that the over response of malic enzyme under protein restriction may be compensatory for the inability of glucose-6-phosphate dehydrogenase to increase.

The activity of enzymes of lipid metabolism is responsive to dietary intake. Therefore, the feeding pattern and accompanying "fress urnal" variations (variation initiated by the ingestion of metabolizable nutrients) are facts that must be considered in interpreting experimental results (6-8,22).

Finally, the length of time the experimental diet is fed to the subjects can influence specific enzyme responses. The majority of dietary studies reported in the literature concern themselves with relatively short term effects, i.e., refeeding following fasting or feeding a high-fat diet following a period of feeding a fat-free diet. Often the experimental observation is made within a period of hours or days following the dietary change. Less frequently, a diet will be fed for a period of several weeks prior to assessing its metabolic impact. Adjustments in the metabolic rate can be achieved by altering enzyme activity by means of metabolic effectors without modifying the amount of enzyme (acute adaptation) or by changing the amount of enzyme protein (chronic adaptation) (1). The half-life for various enzymes can vary from a period of hours to several days. The rate at which a new steady-state level of enzyme activity is achieved is dependent upon its half-life; therefore, those enzymes with short half-lives can change within a few hours after feeding whereas those with longer half-lives will appear to be relatively unchanged (8). It is, therefore, important to measure adaptive enzyme activity at several points over the time period being investigated to determine if a steady-state level of activity has been achieved during the time period of interest. Unless a steady-state level of activity can be demonstrated, generalization of experimental results to longer periods of dietary consumption is unwarranted.

Endocrine-Nutritional Interactions: Relationship to Lipid Metabolism

The endocrine system plays a key role in the metabolic regulation of higher organisms (1). Lipid metabolism is a dynamic process and is the net result of two opposing simultaneous processes, synthesis (fatty acid synthesis and esterification) and degradation (lipolysis and fatty acid oxidation). In general terms, insulin promotes synthetic pathways while catecholamine and glucagon coupled with thyroid hormones promote degradative pathways (23,24). The secretion of several hormones is influenced by the diet (25, 26). Notable among these diet-hormone interactions is the effect of diet on insulin secretion. Insulin secretion occurs following food ingestion. Insulin release is attributed to several factors, among which are the release of gastrointestinal hormones and the rise in plasma glucose and some amino acids (24). Insulin has a positive effect on lipogenesis, lipoprotein lipase, certain aspects of glycerolipid synthesis, and secretion and a negative effect on lipolysis (27-32). The coordinate regulation of lipogenic enzymes of mammalian liver in response to dietary induction involves insulin (33,34). Insulin is required for the dietary induction of acetyl-CoA carboxylase, citrate

cleavage enzyme, malic enzyme, glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, and fatty acid synthetase (34). It would be an oversimplification, however, to state that the effect of diet on the anabolic aspects of lipid metabolism can be explained by the effect of diet on insulin secretion. For example, Rabolli and Martin (25) have demonstrated that the feeding of high-sucrose or high-fat diets known to stimulate or depress, respectively, lipogenesis in rat liver was without effect on plasma insulin levels. Kumar (35) has suggested that dietary components such as fructose can stimulate hepatic lipogenesis in the diabetic rat independently from the effects of insulin, although optimal enhancement of liver fatty acid synthesizing activity required insulin in addition to dietary fructose.

Dietary Effects on Lipid Metabolism

The metabolic pathways and control points for the regulation of lipid metabolism are manifold. The multiplicity and interrelationships of these pathways are depicted schematically in Figure 1. The information provided in this diagram, showing the possible metabolic fates of dietary lipid and carbohydrate, is greatly simplified for purposes of presentation. It should be realized that all of these processes do not occur at the same rate nor do they necessarily occur simultaneously. Only the major organs and predominant pathways are shown. For example, lipogenesis can occur in the skin and intestinal mucosa, and triacylglycerolipid synthesis and lipolysis do occur in the muscle. However, because these are not believed to be major organs of occurrence or major pathways within an organ, they are omitted from Figure 1. Finally, it should be realized that the flux of carbon along any one pathway depends upon whether or not the animal is fed, fasted, rested, or exercising, etc. The dietary inputs shown are fat and carbohydrate. Dietary protein, omitted for simplicity, can also enter the pathway of lipid metabolism via glucose by deamination and gluconeogenesis. Notwithstanding oversimplification, it can be seen from Figure 1 that the processes of lipid metabolism can be conveniently broken down into synthetic and degradative reactions consisting of six major processes: 1) intestinal absorption, 2) uptake of circulating lipoprotein triacylglycerol fatty acids mediated by the enzyme lipoprotein lipase, 3) lipogenesis, 4) esterification (triacylglycerolipid synthesis), 5) lipolysis, 6) fatty acid oxidation, and 7) ketone body metabolism. The influence of diet on each of these pathways will be discussed.

Synthetic Pathways

Intestinal Lipid Absorption. During the process of digestion and absorption, triacylglycerols, monoglycerides, and fatty acids formed by the action of pancreatic lipase enter the intestinal mucosa cell. Some investigators (36) suggest that the diffusion of fatty acid molecules across the unstirred water layer and intestinal brush

border membrane is rate limiting to absorption, whereas others (37,38) suggest that the rate limiting step lies somewhere in the reassembly of triacylglycerols and chylomicron formation within the mucosa cell. Unlike the liver and adipose cell, the predominant pathway for triacylglycerol lipid synthesis is the monoglyceride pathway (2). Fatty acids are absorbed from the gut at varying rates depending upon their degree of saturation and position within the triacylglycerol molecule. This influence upon absorption is believed to be largely a function of micellization prior to absorption into the mucosa cell (39,40). Fatty acyl-CoA ligase, monoglyceride acyl transferase, and diglyceride acyltransferase increase in activity in intestinal microsomes in response to an increased dietary lipid load (41,42). Although the monoglyceride acyltransferase enzyme appears to respond to a lipid load, its activity is unaffected by a 24-hour fast or a four-week protein-free diet, indicating that endogenous proteins of the gut are sufficient to preserve a normal pathway of lipid absorption (43). The chain length and degree of unsaturation of fatty acids influence *in vitro* intestinal triacylglycerol synthesis (44,45). It has been suggested that the specificity of the enzymes of triacylglycerol synthesis contributes to the portioning of fatty acids between portal blood and chyle (44). Bennett-Clark (37) has demonstrated that addition of medium chain triacylglycerols (MCT) to long chain triacylglycerols (LCT) during duodenal infusion decreased the output of LCT in thoracic duct lymph. Octanoic acid also reduced triacylglycerol synthesis from oleic acid in slices of rat jejunum (37). These observations suggest that the quantity of fat and its composition can influence both the rate at which it is absorbed and the rate at which it is resynthesized into triglyceride.

Uptake of Triacylglycerol Fatty Acid from Plasma Lipoproteins.

Extrahepatic removal of chylomicron and very low density lipoprotein triacylglycerol fatty acid is mediated by the hydrolytic action of the enzyme lipoprotein lipase (LPL) acting at the capillary endothelium (46). Through changes in LPL activity, the flow of fatty acids from plasma lipoprotein triglycerides into tissues is altered according to the requirements of the different tissues (47). The directional nature of LPL is illustrated by an increase in adipose tissue LPL in the fed state and a decrease in the fasted state (48). Mammary gland LPL activity increases dramatically at parturition coinciding with the need for increased uptake of blood triacylglycerols for the synthesis of milk lipids (49). The increase in mammary LPL activity at parturition is also accompanied by a decrease in adipose tissue LPL resulting in a diversion of chylomicron lipids from one tissue to the other (50). The three types of dietary alterations most studied in connection with LPL activity are fasting-refeeding, high-carbohydrate, and high-fat feeding. Fasting exerts the following effects on LPL activity in the following tissues: no change, lung; increase, heart and red skeletal muscle; and decrease, adipose tissue (48,51-53). Although glucose feeding increases adipose tissue LPL activity, Harris and Felts (54) found that the

overall effect of a high-carbohydrate diet may be to decrease the removal rate of plasma chylomicron triglyceride (Figure 2). The reduced clearance rate for chylomicron triglyceride fatty acids, when rats were fed a high-carbohydrate diet, may result from an alteration in the rates of muscle and adipose LPL activity. The effect of fasting, feeding a high-fat diet or feeding a high-carbohydrate diet on the relative activities of adipose, skeletal muscle and heart LPL activities is shown in Figure 3 (55). It can be seen that while feeding a high-carbohydrate diet does result in high adipose tissue LPL activity, muscle and heart LPL activities are reduced compared to the activities seen after fat feeding. The tissue LPL pattern in fat feeding resembles that seen in fasting. The regulatory mechanism whereby LPL is influenced by dietary carbohydrate and fat in a tissue-specific manner is not known but is probably related to diet-induced hormonal responses. LPL responds to insulin in a tissue-specific manner. Borensztajn et al. (56) have demonstrated that insulin increases adipose tissue LPL but is without effect on heart LPL, which suggests that the LPL of each tissue may be distinct and regulated differently or the regulatory mechanism within the cell may be selectively responsive to various stimuli (55,56).

The effect of specific types of dietary fats or carbohydrates on LPL activity has received little attention. A fatty acid specificity for LPL has not been convincingly demonstrated; however, the possibility that the degree of unsaturation of dietary fat may influence LPL activity has been suggested (57,58).

Lipogenesis. Up to this point, most of the discussion has centered about the absorption and uptake of fatty acids originating from the lipid portion of the diet. In addition to obtaining fatty acids preformed from the diet, the mammalian organism has the ability to synthesize fatty acids from any substance capable of yielding acetyl-CoA. In animals consuming a mixed or high carbohydrate diet, the primary source of carbon for fatty acid synthesis is glucose derived from the carbohydrate portion of the diet. A large portion of dietary carbohydrate calories follows the metabolic flux: carbohydrates \rightarrow fatty acids \rightarrow CO_2 + H_2O . The degree to which dietary carbohydrates are utilized for fat synthesis depends upon several factors such as the amount of fat and carbohydrate in the diet, and the caloric balance of the animal. Dietary carbohydrates replenish liver and muscle glycogen and serve as substrates for energy requiring processes such as brain metabolism and muscular contraction. Dietary carbohydrate intake above these immediate energy requirements is converted via the process of lipogenesis to fatty acids. As mentioned previously, not all animals are alike with respect to which organ is primary in fatty acid synthesis. The rat can synthesize fatty acids from glucose to a significant extent in both the liver and adipose tissue, although under most dietary situations the adipose organ seems to predominate (59). In avian species, the liver is the main organ of lipogenesis; while in swine,

adipose tissue is predominant (60-62). The human appears to synthesize the bulk of its fatty acids in the liver with adipose tissue contributing an insignificant amount of de novo synthesized fatty acids (14,63).

The influence of diet on lipogenesis has been the subject of numerous investigations. Certain conclusions can be drawn concerning diet and lipogenesis, i.e., lipogenesis is increased following fasting and refeeding and depressed following the feeding of a high-fat diet; however, it is apparent that the metabolic effects of other dietary treatments are more controversial (64). Comparison and interpretation of studies on diet and lipogenesis are complicated by the following experimental variables: species of animal; site of lipogenesis; quantity and composition of the fat or carbohydrate portion of the diet; prior dietary regimen; length of time the diet was fed; composition of the control diet selected for comparison; the substrate utilized in the in vitro assay; etc. (4,12,14,15,17,40,60,65-74). These considerations make it impossible to state unequivocally, for example, that dietary fructose increases lipogenesis. An example may serve to illustrate this point. Romsos and Leveille (15) studied the effect of dietary fructose on in vitro and in vivo fatty acid synthesis in the rat. The interpretation of the dietary effect depended upon the substrate (glucose or fructose) and concentration selected for the measurement of in vitro lipogenesis (Figure 4). The metabolic situation was clarified when in vivo fatty acid synthesis was measured by injecting $^3\text{H}_2\text{O}$ and measuring ^3H incorporation into liver fatty acids (Figure 5). The incorporation of ^3H was a measure of fatty acid synthesis that was independent of the substrate being utilized. Fructose fed rats had a significantly greater rate of hepatic lipogenesis. However, measuring lipogenesis in the rat requires extra-hepatic estimates of fatty acid synthesis before the effect of diet on the entire animal can be evaluated. Adipose tissue is also a prime organ of fatty acid synthesis in the rat. Romsos and Leveille (15) found that lipogenesis in adipose tissue was decreased by fructose (as compared to the increase seen in liver), and had a net balancing effect upon total rat lipogenesis. Figure 6 shows that feeding fructose was without a significant effect on ^3H incorporation into total body fatty acids (liver + carcass). While the total body capacity of the rat to synthesize fatty acids was unchanged, the relative importance of the liver increased and that of extra-hepatic tissues decreased when fructose, rather than glucose, was fed to rats.

Another example of a differential effect of diet on liver and adipose tissue lipogenesis is seen when dietary unsaturated fat is fed to rats (17). In this case, the lipogenic activity of adipose tissue increased when safflower oil was fed and hepatic lipogenesis decreased (Figure 7) illustrating that safflower oil feeding caused a shift in organ lipogenesis of an opposite nature to that seen with fructose feeding. Other dietary additives such as butanediol,

hydroxycitrate, or orotic acid influence lipogenesis by decreasing hepatic fatty acid synthesis, but leave adipose tissue fatty acid synthesis relatively unaffected or increased (16,75-78). These results further emphasize that there are organ-specific as well as species-specific metabolic responses to various dietary factors:

To summarize, numerous factors should be considered in the evaluation of the effect of diet on lipogenesis. However, certain generalizations appear justified: 1) fasting decreases lipogenesis, 2) refeeding a high carbohydrate diet following fasting elicits a greater increase in lipogenesis than that elicited when a high fat diet is fed, 3) dietary sucrose is hyperlipogenic; partially due to its fructose content and partially due to an unspecified specific disaccharide effect, 4) unsaturated fat depresses liver lipogenesis and increases adipose tissue lipogenesis in the rat but not the chick, and 5) in the rat, liver and adipose lipogenesis often responds differently to diet.

Triacylglycerol Synthesis. The primary storage form of excess dietary energy is the triacylglycerol molecule. Both dietary and de novo synthesized fatty acids contribute to the fatty acids esterified to the glycerol molecule. The glycerol moiety can be derived from glucose via the action of sn-glycerol-3-phosphate dehydrogenase on dihydroxyacetone phosphate resulting in the formation of sn-glycerol-3-phosphate, the fatty acyl acceptor molecule; sn-glycerol-3-phosphate can also be formed directly from glycerol by the action of the enzyme glycerolkinase. Tissues such as the liver can derive sn-glycerol-3-phosphate from both sources while adipose tissue possesses very low glycerolkinase activity and relies primarily on the generation of triose phosphate for its supply of acyl acceptor. The primary pathway of triacylglycerol synthesis by liver and adipose tissue is the sn-glycerol-3-phosphate pathway (9). The liver can also utilize dihydroxyacetone phosphate as an acyl acceptor; however, the dihydroxyacetone pathway is probably of minor importance in the biosynthesis of hepatic glycerolipids (79). Triacylglycerol synthesis by the intestinal mucosa is via the monoglyceride pathway as has been discussed previously under Intestinal Lipid Absorption:

Lamb and Fallon (80) have studied microsomal hepatic triacylglycerol biosynthesis from sn-1,3-[¹⁴C]glycerol-3-phosphate and suggest that the rate-limiting enzyme of this pathway is phosphatidate phosphohydrolase, catalyzing the formation of diacylglycerol from phosphatidic acid (Table 1) (80). Other enzymes involved in triacylglycerol synthesis either catalyze their particular reaction at a high rate compared to phosphatidate phosphohydrolase or change their activity only slightly when the overall rate of triacylglycerol formation is known to be increased or decreased. Such enzymes appear to be of constitutive nature and probably are not important determinants of the overall rate of the pathway.

Table 1
Hepatic Microsomal Triacylglycerol Biosynthesis
from
sn - 1,3 - [14 C]Glycerol-3-phosphate¹

Intermediate of Reaction	Enzyme	Maximum in vitro rate: nmoles/min/mg microsomal protein
sn-Glycerol-3-P		
↓	sn-Glycerol-3-P acyltransferase	6.0
Lysophosphatidate		
↓	1-Acyl-sn-glycerol- 3-P-acyltransferase	35.0
Phosphatidate		
↓	Phosphatidate phosphohydrolase	1.0
Diacylglycerol		
↓	Diacylglycerol acyltransferase	6.0
Triacylglycerol		

¹Data from Lamb and Fallon (80)

Triacylglycerol formation is responsive to dietary alterations while phospholipid synthesis is not greatly altered by diet (81). Triacylglycerol formation is influenced by the quantity and composition of the diet as shown in Figure 8. Fallon and Kemp (82) found that hepatic triacylglycerol synthesis from sn-glycerol-3-phosphate was markedly reduced by 48 hours of fasting, relatively unaffected by feeding a 40% corn-oil diet, and dramatically increased when 64% of the diet came from starch, glucose, or fructose. Diets high in sucrose or fructose result in a greater rate of glycerolipid synthesis than when a similar amount of starch is fed (11,82-84). Increased triacylglycerol synthesis may be related to the increased rate of lipogenesis, availability of sn-glycerol-3-phosphate, or due to an insulin effect on the enzymes of the sn-glycerol-3-phosphate pathway (9,84-86). Although it logically follows that dietary

treatments that increase lipogenesis should result in increased triacylglycerol formation, under certain conditions, triacylglycerol synthesis appears to be regulated separately from lipogenesis. Feeding high-fat, and particularly unsaturated fat, depresses hepatic lipogenesis, yet similar diets do not depress the capacity of the liver for triacylglycerol formation (11,82,87,88). Triacylglycerol formation has not been demonstrated to be influenced by the origin of the fatty acid moieties (de novo from glucose or preformed from the diet).

The availability of the acyl acceptor, phosphatidic acid, does not appear to be the predominant controlling factor in triacylglycerol synthesis. Groener and Van Golde (83), utilizing isolated hepatocytes from fed and 48-hour fasted rats, could find no difference in hepatocyte phosphatidic acid levels while triacylglycerol synthesis was depressed 80%. Further evidence that phosphatidic acid formation is not the sole controlling factor in triacylglycerol formation is provided by examining the activities of glycerolkinase and sn-glycerol-3-phosphate dehydrogenase under the conditions of fasting and carbohydrate feeding. Fasting increased the activities of these enzymes while carbohydrate feeding decreased them (89,90). An opposite effect might have been predicted if the formation of phosphatidic acid was closely related to triacylglycerol synthesis. The activity of the acyltransferase enzymes also does not correlate well with the overall rate of triacylglycerol synthesis either, although some investigators believe the relative activities of the sn-glycerolphosphate acyltransferase and carnitine palmityltransferase may influence the fate of fatty acids in the cell (82,88,91).

Some of the known effects of diet on enzymes related to hepatic triacylglycerol synthesis are shown in Table 2. It is apparent that the effect of diet on triacylglycerol synthesis has not received the degree of attention that it has in connection with lipogenic enzymes. It is also apparent that, like lipogenesis, conflicting results concerning the effect of diet on triacylglycerol synthesis appear in the literature. Fallon and Kemp (82) found that feeding high-carbohydrate or high-fat diets to rats for six days increased the activity of hepatic glycerolphosphate acyltransferase but triglyceride synthesis from sn-¹⁴C glycerol-phosphate was unchanged by the high-fat diet and increased by the high-carbohydrate diet. In contrast, Aas and Daas (92) found that hepatic glycerolphosphate acyltransferase was decreased in the rat by feeding a high-fat diet for two days. Wiegand et al. (88) found hepatic glycerolphosphate acyltransferase unresponsive to varying levels (0-15%) of dietary fat fed for seven days. Askew et al. (87) fed a high-fat or high-carbohydrate diet for a period of 28 days and found that hepatic glycerolipid synthesis was unaltered by the high-fat diet but was decreased by the high-carbohydrate diet. The results of these studies indicate that the level of dietary fat or carbohydrate, length of time the diet is fed, and

Table 2
Effect of Nutritional Factors on Enzyme Reactions Leading to Hepatic Triacylglycerol Synthesis¹

Substrate of Reaction	Enzyme	Fasting	Fasting	Fat	Carbohydrate
		Refeeding	Refeeding	Feeding	Feeding
Fatty Acid	Fatty Acyl-CoA synthetase	++93	++93	+93	+93
Glycerol	Glycerolkinase	+90	+90	+89, 90	+89
Dihydroxy-acetone-P	sn-Glycerol-3-phosphate dehydrogenase	+90	*	+90	+90
sn-Glycerol-3-P	sn-Glycerol-3-phosphate acyltransferase	+92++82	+91	++88 +92 +82, 97	+82, 94
Lysophosphatidate	1 Acyl-sn-glycerol- 3-phosphate acyltransferase	*	*	*	*
Phosphatidate	Phosphatidate phosphohydrolase	+95	*	*	+94
Diacylglycerol	Diacylglycerol acyltransferase	*	*	*	*
Triacylglycerol Synthesis (overall formation)	Includes all of the above	+81-83	+81, 83	++82, 87	+82, 94, 96 +87

¹ + = increase, - = decrease, ++ = no change, * = no information available. Numbers refer to references.

the indicator of triacylglycerol synthesis are critical factors in assessing the influence of diet on triacylglycerol synthesis.

The influence of diet on triacylglycerol synthesis in organs other than the liver has received much less attention. It is not clear if triacylglycerol synthesis in muscle and adipose tissue follows a similar adaptive pattern to that seen in liver.

Degradative Pathways

Lipolysis. Fatty acids are mobilized from adipose depots in response to a negative energy balance, such as that created by exercise or fasting (98). The rate at which fatty acids are mobilized determines their availability to the liver and muscle and appears to be an important determinant of the overall rate of oxidative metabolism (99,100). Diet can influence lipolysis by its prior influence on the fatty acid composition of adipose tissue or by a more direct effect on the lipolytic process itself (101-106).

Although the fatty acid composition of adipose tissue reflects to a large degree the fatty acid composition of the diet, it can not be assumed that fatty acid release will in turn reflect adipose tissue fatty acid composition (101). For example, lauric acid appears to be less easily mobilized than longer chain fatty acids (101). Lipolysis in adipose tissue from rats fed diets rich in linolenic acid is greater than in rats fed diets high in linoleic acid (102). Differential mobilization of adipose fatty acids probably reflects the specificity of the lipolytic enzymes for fatty acids esterified at certain positions in the triacylglycerol molecule which in turn reflects the specificity of the acyltransferases involved in triacylglycerol formation (101). Although it has been suggested that unsaturated fats are oxidized *in vivo* at greater rates than saturated fats (see following section on fatty acid oxidation), Demarne et al. (107) could find no evidence of preferential catabolism of linoleic acid during energy restriction following the feeding of a sunflower-seed oil diet that elevated the linoleic acid content of adipose tissue to 45%.

Fasting increases the sensitivity of adipose tissue to the lipolytic action of epinephrine whereas fat feeding decreases the same response, possibly through decreased epinephrine activated adenylyl cyclase activity (103-106). Dietary fat also produces alterations in fat cells that decrease insulin binding and membrane glucose transport, which suggests that fat feeding modifies the plasma membrane of the fat cell (108,109). Ogundipe and Bray (110) found that isocaloric substitution of fat for carbohydrate in the diet of the rat impaired the response of fat cells to insulin independent of any effects of diet on cell size, whereas lipolysis was influenced mainly by cell size. Their results suggested that substitution of dietary fat for carbohydrate had little influence on lipolysis. The

difference between the results as reported by Ogundipe and Bray (110) and other investigations (103-105), of the influence of dietary fat on lipolysis, may be related to the level of fat fed.

It is apparent that diet can exert an effect upon lipolysis through its effect on the nature of the fatty acids deposited previously in the adipose depots and through alterations in hormone responsiveness mediated by plasma membrane binding sites or adenyl cyclase activity. It is not known if dietary induced changes in the fatty acid complement of adipose tissue triglycerides have a significant physiological effect on the rate of mobilization of fatty acids.

Fatty Acid Oxidation. It is well-established that fasting or feeding high-fat diets decreases the respiratory quotient (RQ), which indicates an increased oxidation of fat. In vivo and in vitro experiments have established that fat feeding and fasting promote fatty acid oxidation and decrease glucose oxidation while high carbohydrate diets are accompanied by decreased fatty acid oxidation and increased glucose oxidation (111-116). The metabolic pattern seen in starvation is similar to that accompanying fat feeding, undoubtedly due to the heavy reliance upon fat as an oxidative energy source in both situations. A comparison of oxidative metabolism in vivo in starved, fat-fed and carbohydrate-fed rats is shown in Figure 9. Mayes and Felts (116) fed either a 90% carbohydrate (by weight) diet or a diet with an isocaloric amount of butterfat substituted for the carbohydrate portion of the diet. The diets were fed for a one-week period. Starved rats were denied access to food for 48 hours prior to the experiment. The rats were injected intravenously with either [1-¹⁴C] acetate, [1-¹⁴C] palmitate, or [U-¹⁴C] glucose and expired ¹⁴CO₂ was trapped and counted over a three-hour period. The interpretation of in vivo radioisotope experiments such as these are complicated by plasma substrate specific activity considerations; however, these considerations were estimated by the authors (116) to be minimal in this particular experiment. The fat-fed and starved rats oxidized a greater percent of the injected fatty acid to CO₂ than carbohydrate fed rats. Conversely, the carbohydrate-fed rats oxidized more glucose than fat-fed or starved rats. The lack of effect of starvation or fat feeding on acetate oxidation deserves some comment. Bringolf et al. (117) incubated rat diaphragm muscle from high-fat or high-carbohydrate fed rats with acetate-¹⁴C as a substrate and found no difference in acetate oxidation. A similar lack of effect attributable to diet on TCA cycle enzymes has been reported by Dohm et al. (118) and Askew et al. (119). In those studies, feeding diets containing 9.6, 40.1, or 82.9% of the caloric energy from fat for four weeks had no significant dietary effect on mitochondrial yield, citrate synthetase, isocitrate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, or cytochrome oxidase in the rats. The lack of effect of high-fat or high-carbohydrate diets on the oxidative metabolism of acetate suggests that

diet-related effects are exerted prior to the entry of acetate into the TCA cycle. Bringolf et al. (117) found that fat feeding decreased pyruvate oxidation by rat diaphragm indicating that fat feeding may decrease glucose oxidation by inhibition of pyruvate dehydrogenase. Although experimental evidence is lacking, the acceleration of fatty acid oxidation in fat fed or starved rats may be accomplished by an increased activation, or transport of fatty acid across the mitochondrial membrane. Dietary fat could also exert an effect on the activities of the enzymes of β -oxidation; however, Askew et al. (119) found only a small increase in skeletal muscle mitochondrial palmitylcarnitine oxidation in fat-fed rats, which indicates that dietary fat may exert an effect on fatty acid oxidation at or prior to palmitylcarnitine transport across the mitochondrial membrane.

The effect of diet on fatty acid oxidation has been largely confined to the study of high-fat or high-carbohydrate diets or starvation. The influence of dietary carnitine on lipid metabolism has received some attention due to the obligate role of this compound in fatty acid oxidation. Fatty acid oxidation is increased in rats exposed to chronic daily exercise (120). Theorizing that tissue levels of carnitine might be limiting under conditions of chronic high level fat oxidation such as exercise, Askew et al. (121) fed exercising rats diets supplemented with 0.5% L-carnitine. Although exercise increased adipose tissue fatty acid turnover, supplemental dietary carnitine neither increased skeletal muscle *in vitro* fatty acid oxidation nor further enhanced the turnover rate of adipose tissue, which indicates that tissue carnitine levels are probably adequate to support fatty acid oxidation in exercising animals.

Not all fatty acids are oxidized at the same rate. Unsaturated fatty acids have been reported to be oxidized to CO_2 at rates faster than saturated fatty acids, both *in vivo* and *in vitro* (122-129). Not all reports agree, however. Other investigators (120,130-135) have found little or no differences in the relative oxidation rates of different fatty acids. Mathias et al. (136) have noted that changes in pool size, difference in absorption rates and competing metabolic side reactions might account for the conflicting reports of differences in fatty acid oxidation *in vivo*. *In vitro* studies are similarly influenced by incubation conditions, tissue source, and position of the radiocarbon label in the fatty acid substrate (136,137). The relative rapidity with which structurally different fatty acids are mobilized and oxidized as energy sources has not been adequately investigated to permit conclusions as to the influence of dietary fatty acids on fatty acid oxidation.

Ketone Body Metabolism. Ketone body metabolism has been studied principally under the conditions of starvation, diabetes, fat feeding, and exercise (119,138-142). Under these conditions, the concentration of acetoacetate and β -hydroxybutyrate increase in the

blood, indicative of ketogenesis from fat. Ketones are readily metabolized to CO_2 by extrahepatic tissues such as the heart, kidney, and skeletal muscle and under appropriate circumstances can serve as important respiratory fuels (23,143). The two major ketone bodies produced by the liver are acetoacetate and β -hydroxybutyrate (23). Ketone bodies are transported via the blood to extrahepatic tissues for oxidation, as shown in Figure 10. The liver does not oxidize ketone bodies due to the lack of the first enzyme involved in acetoacetate utilization, 3-oxoacid-CoA transferase (23,143). The rate-limiting reaction of ketone body production is believed to be that catalyzed by hydroxymethylglutaryl-CoA synthetase (Figure 10) (143). The corresponding rate-limiting enzyme of ketone body oxidation has not been identified, although β -hydroxybutyrate dehydrogenase has been suggested as a rate-limiting enzyme under certain conditions (142). The activity of 3-oxoacid-CoA transferase is unique to the oxidative pathway and increases in certain extrahepatic tissues under the conditions of starvation, fat feeding, and exercise - three conditions known to increase ketone body formation and utilization (119,138,141,142). It is not clear whether or not the production of ketones by the liver and their utilization by extrahepatic tissues are controlled by the supply of fatty acids to the liver or by the liver's capacity to convert fatty acids into acetoacetate and β -hydroxybutyrate. McGarry and Foster (144) believe that both aspects are important and have proposed a two site concept for the control of ketogenesis. The mobilization of fatty acids from adipose tissue (site 1) is facilitated by a fall in plasma insulin while a rise in plasma glucagon increases ketogenesis by the liver (site 2). Elevation of liver carnitine content and depletion of glycogen stores coupled with activation of the carnitine acyltransferase reaction are essential features of this proposal. The major pathways of fatty acid metabolism in the liver are shown in Figure 11. According to McGarry and Foster (144), the basic difference between livers of low and high ketogenic potential is that in the former a fatty acid load is disposed of primarily via reaction sequence 1 (Figure 11) while in the latter a greater flux occurs via reactions 2 and 3.

The activity of several key enzymes of the ketogenic and oxidizing pathways depicted in Figure 10 are responsive to the amount of fat in the diet. The response of liver hydroxymethylglutaryl-CoA synthetase and skeletal muscle 3-oxoacid-CoA transferase to diets containing 9.6, 40.1, and 82.9% of the calories as fat is shown in Figure 12. The activity of liver hydroxymethylglutaryl-CoA synthetase increased as the proportion of fat in the diet increased. Muscle 3-oxoacid-CoA transferase activity was reduced in the low-fat, high-carbohydrate diet but was similar in the intermediate (control) and high-fat diets, which suggests that this enzyme is less responsive to total dietary fat content than liver hydroxymethylglutaryl-CoA synthetase.

In summary, the influence of diet on ketone body production may be shared by its influence on the fat load provided the liver and the liver's ability to partition fatty acids among esterification, oxidation and ketogenesis. Oxidation of ketone bodies by extrahepatic tissues is a function of the concentration of ketone bodies in the blood and the activities of the enzymes of ketone body oxidation.

CONCLUSIONS

Because the topic of this review was rather broad, it was necessary to omit many pertinent examples of the effect of diet on lipid metabolism. Brevity and adherence to the general review nature of this topic also prevented in-depth discussion of underlying hormonal and cellular control mechanisms. It is hoped that through the specific examples cited illustrating the effect of diet on lipid metabolism the reader might gain an appreciation of the diversity of metabolic effects that can result from relatively simple dietary alterations.

RECOMMENDATIONS

None.

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Figure 1. Schematic illustration of the interrelationships of synthetic and degradative pathways of lipid metabolism following the ingestion of carbohydrate and fat. Only major organs and pathways are shown. Not all processes depicted occur simultaneously or at the same rate.

Figure 2. Effect of fasting or consuming a high-fat or high-carbohydrate diet on the half-lives of removal of chylomicron triacylglycerol fatty acids in the rat. Rats were fed either a control (fasted rats), 65% dextrose (carbohydrate-fed rats), or a 50% butterfat (fat-fed rats) diet for 14 days. Food was removed from the fasted rats 18 to 20 hours before the experiment. One to two hours before the experiment all animals were intubated; the fasting rats received 4 ml water, the carbohydrate-fed rats received 4 ml of a 10 % solution of corn starch, and the fat-fed rats received 4 ml of evaporated milk. The radioactivity in $D < 1.006$ lipoproteins resulting from infusion of ^{14}C -labeled chylomicron preparations was monitored and the half-life calculated from the disappearance portion of the plasma radioactivity-time curve. Values shown represent the mean \pm SEM for 4 - 6 rats per group. [Data from Table 2, Harris and Felts (54).]

Figure 3. Effect of fasting, fat feeding or carbohydrate feeding on activities of rat adipose tissue, skeletal muscle, and heart lipoprotein lipase (LPL). Rats were fed a stock diet (fasted), 50% butterfat (fat-fed) or 65% dextrose (carbohydrate-fed) for 14 days. Food was removed from the fasted rats 18 to 20 hours before tissue lipoprotein lipase determinations. Lipoprotein lipase activity was determined on acetone-ether powders of retroperitoneal adipose tissue, biceps femoris muscle, and heart. Enzyme activities are represented by the length of the arrow and are the mean values of 9 - 16 rats per group. Units of lipoprotein lipase activity are shown beneath the figures. [Data from Table 2, Delorme and Harris (55).]

Figure 4. Effect of dietary glucose or fructose on in vitro hepatic lipogenesis from $[\text{U-}^{14}\text{C}]$ glucose or $[\text{U-}^{14}\text{C}]$ fructose in the rat. Rats were fed diets containing 66.1% glucose or fructose for 4 weeks. Lipogenesis was measured in liver slices. Values shown represent the mean \pm SEM for 4 rats per group. The levels of significance is shown above each pair of bars. [Data from Table 1, Romsos and Leveille (15).]

Figure 5. Effect dietary glucose or fructose on in vivo hepatic lipogenesis in the rat. Rats were fed diets containing 66.1% glucose or fructose for 3 weeks. Rats were injected with 2 mCi of $^3\text{H}_2\text{O}$ and killed 20 min later. Values shown represent the mean \pm SEM for 10 rats per group. The level of significance is shown above the bars. [Data from Table 6, Romsos and Leveille (15).]

APPENDIX

Figure 6. Effect of dietary glucose or fructose on total in vivo lipogenesis in the liver and carcass of the rat. Rats were fed diets containing 66.1% glucose or fructose for 3 weeks. Rats were injected with 2 mCi $^3\text{H}_2\text{O}$ and killed 20 min later. Values shown represent the mean \pm SEM for 10 rats per group. N.S. = not significantly different group. N.S. = not significantly different, $p > 0.05$. [Data from Table 7, Romsos and Leveille (15).]

Figure 7. Effect of dietary tallow or safflower oil on in vitro hepatic and adipose tissue lipogenesis in the rat. Rats were fed diets containing either 18.5% tallow or safflower oil for 22 days. Lipogenesis was determined by a tissue slice procedure. Values shown represent the mean \pm SEM for 17 rats per group. Level of significance is shown above each pair of bars. [Data from Table 2, Waterman et al. (17).]

Figure 8. Effect of fasting and diet on hepatic triacylglycerol synthesis in the rat. Rats were fed a lab chow diet for 6 days (control) and subsequently fasted for 48 hours (fasted) or fed a 40.5% corn oil diet (high-fat), 64% potato starch (high-starch), 64% glucose (high-glucose), or 64% fructose (high-fructose) for 7 days. Triacylglycerol synthesis was measured in vitro by the incorporation of sn-1,3- ^{14}C -glycerol-3-phosphate into triacylglycerol by liver homogenates. Values shown are expressed as percent of control. Control value for the fasted vs. control comparison was 1.48 CPM/ μg protein, for all other comparisons the control value was 0.86 CPM/ μg protein. All comparisons with the control value were significantly different, $P < 0.01$. [Data from Tables 1 & 3, Fallon and Kemp (82).]

Figure 9. Effect of fasting, fat-feeding and carbohydrate-feeding on in vivo $[1-^{14}\text{C}]$ acetate, $[1-^{14}\text{C}]$ palmitate, and $[1-^{14}\text{C}]$ glucose oxidation in the rat. Rats were fed a stock diet and subsequently fasted for 48 hours (starved) or fed for one week a 40% corn starch plus 50% glucose diet (carbohydrate-fed) or a diet with an isocaloric amount of butterfat substituted for the starch and glucose (fat-fed). Rats were injected via the tail vein with 2 μCi of the radioactive substrate indicated. $^{14}\text{CO}_2$ was trapped and counted over a three-hour period. Results are expressed as mean \pm SEM percent of injected dose recovered after 3 hours for 3 - 6 rats per group. [Data from Mayes and Felts (116).]

Figure 10. Schematic outline of ketone body metabolism. Enzymes corresponding to the numbered steps are: 1. Enzymes of β -oxidation; 2. Acetoacetyl-CoA thiolase; 3. Hydroxymethylglutaryl-CoA synthetase; 4. Hydroxymethylglutaryl-CoA lyase; 5. 3-Hydroxybutyrate dehydrogenase; 6. 3-oxoacid-CoA transferase; 7. Acetoacetyl-CoA thiolase; and 8. Enzymes of the TCA cycle. [After Bates et al. (139).]

Figure 11. Pathways of fatty acid metabolism in the liver. Reaction 1: fatty acid esterification to form triacylglycerols, 2 and 3, transfer mechanism involving the sequential action of carnitine acyltransferase I on the outer aspect of the inner membrane (reaction 2) and carnitine acyltransferase II on the inner aspect of the membrane (reaction 3). [From McGarry and Foster (144), Copyright 1977, American Medical Association, used with permission.]

Figure 12. Effect of varying levels of dietary fat and carbohydrate on the *in vitro* activities of hepatic hydroxymethylglutaryl-CoA synthetase and gastrocnemius muscle 3-oxoacid-CoA transferase in the rat. The high-carbohydrate diet contained 9.6%, the control diet contained 40.1%, and the high-fat diet 82.9% of the total dietary kcal as fat. Rats were fed the diets for 4 weeks. Values shown represent the mean \pm SEM for 31 - 35 rats per group. All three diets gave significantly different liver synthetase activities, $P < 0.0001$, whereas in the muscle the control and high-fat transferase activities were similar but both greater than that in the high-carbohydrate group, ($P < 0.0001$). [Data from Tables 3 & 5, Askew et al. (119).]

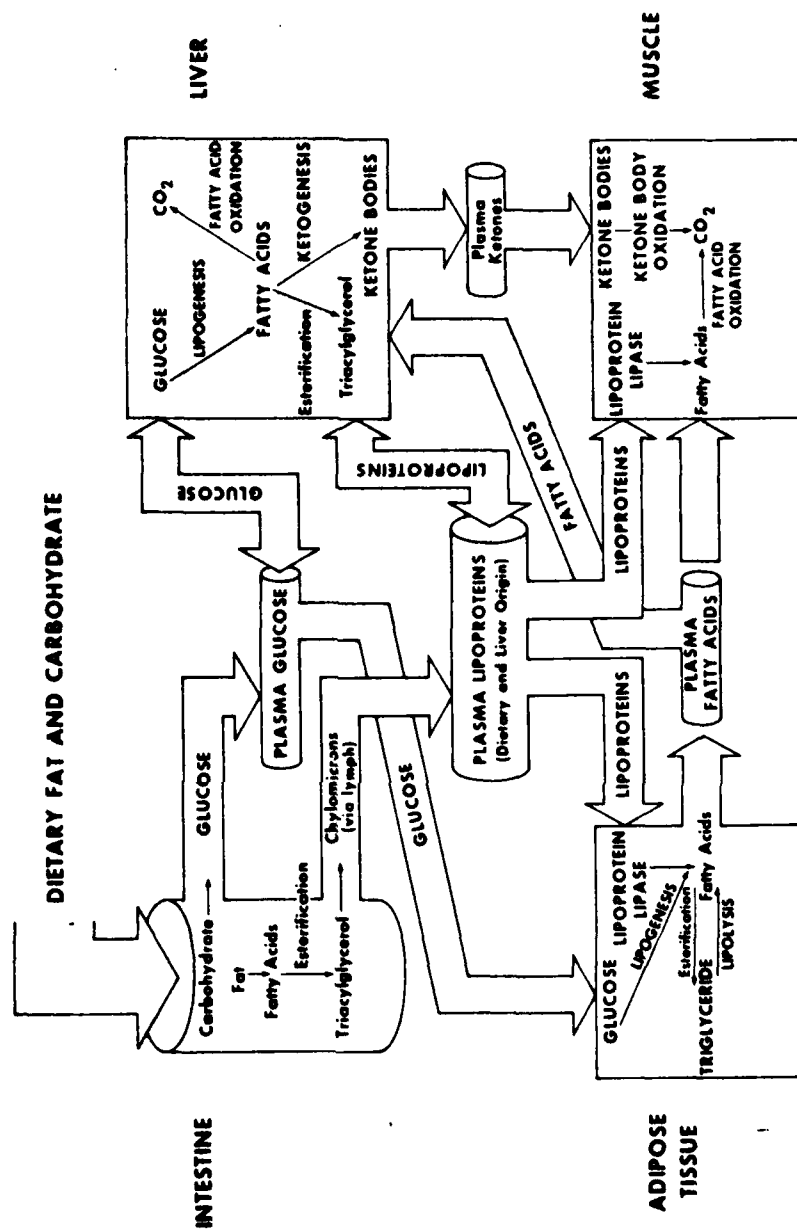


Figure 1

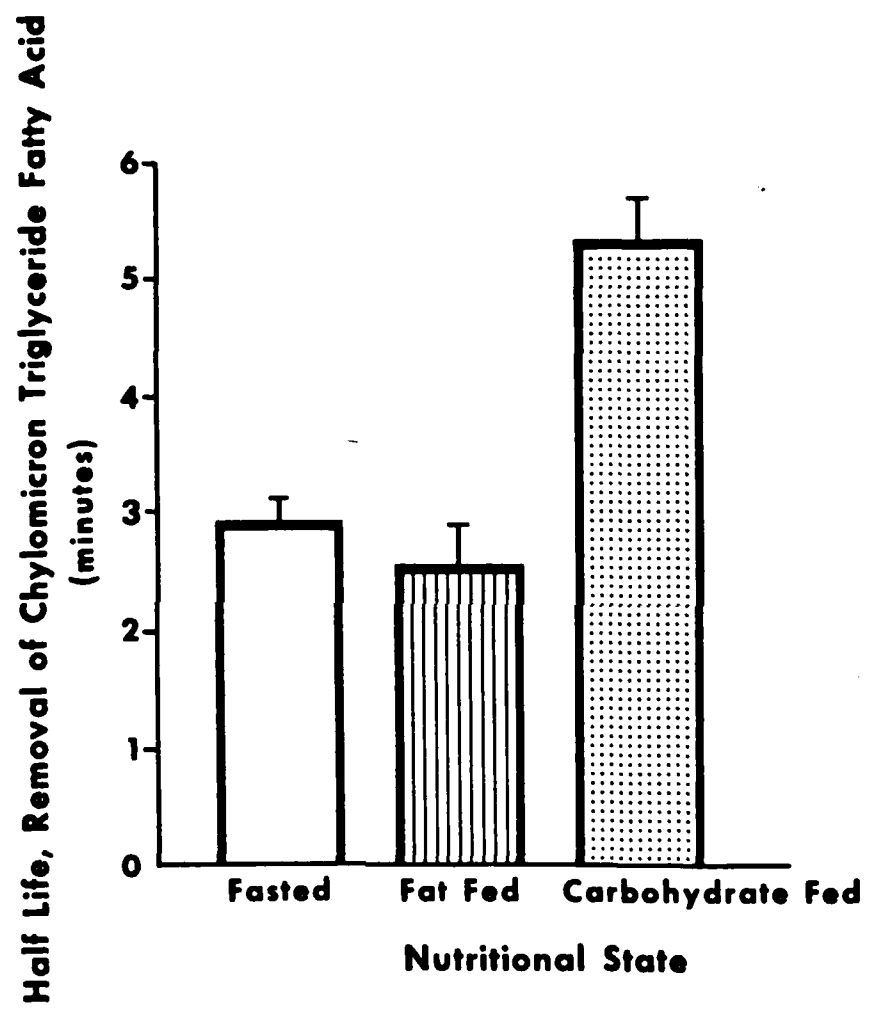


Figure 2

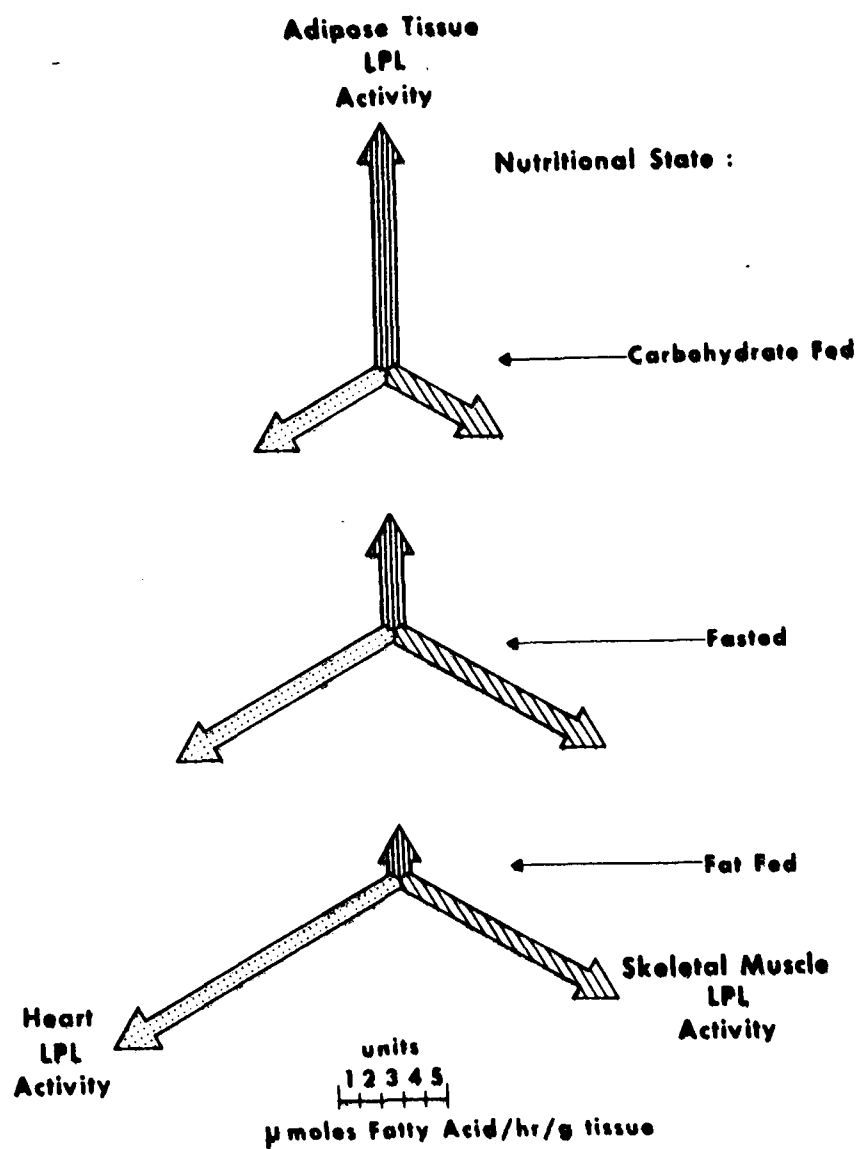


Figure 3

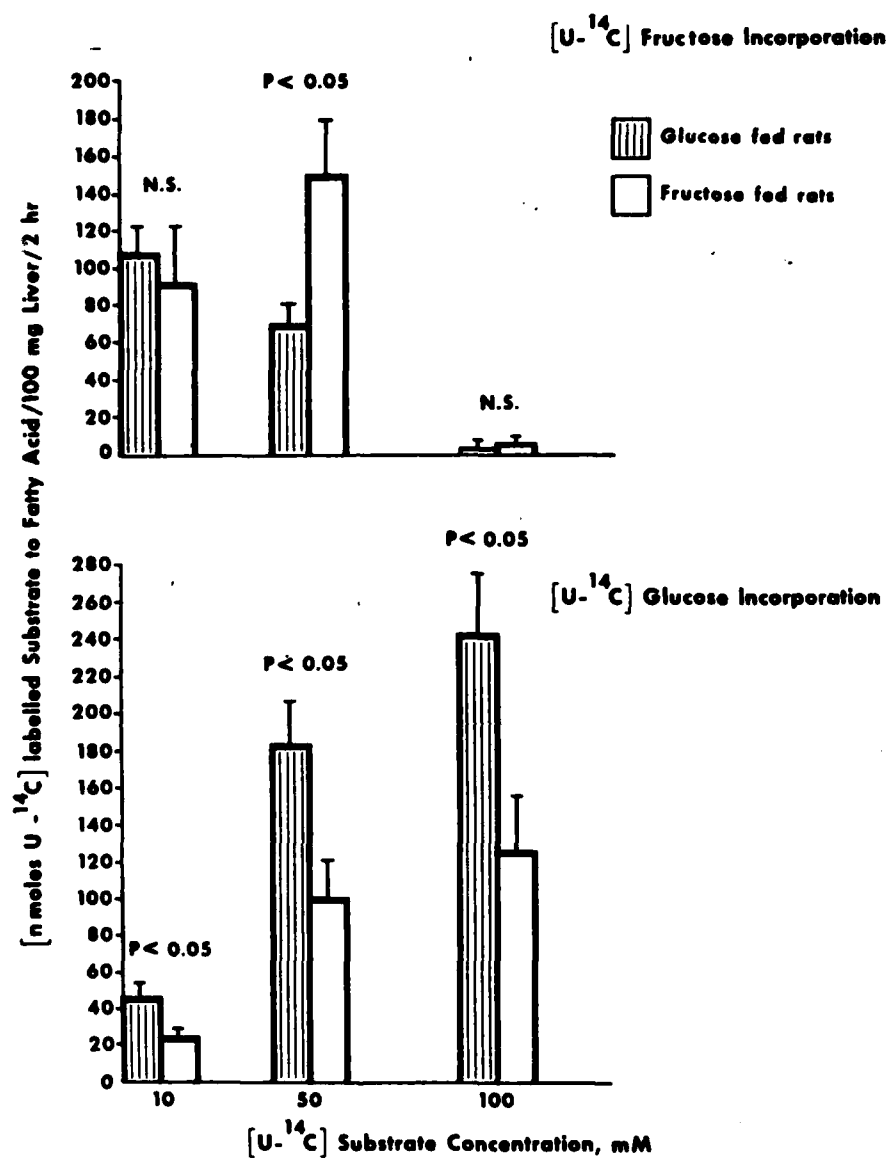


Figure 4

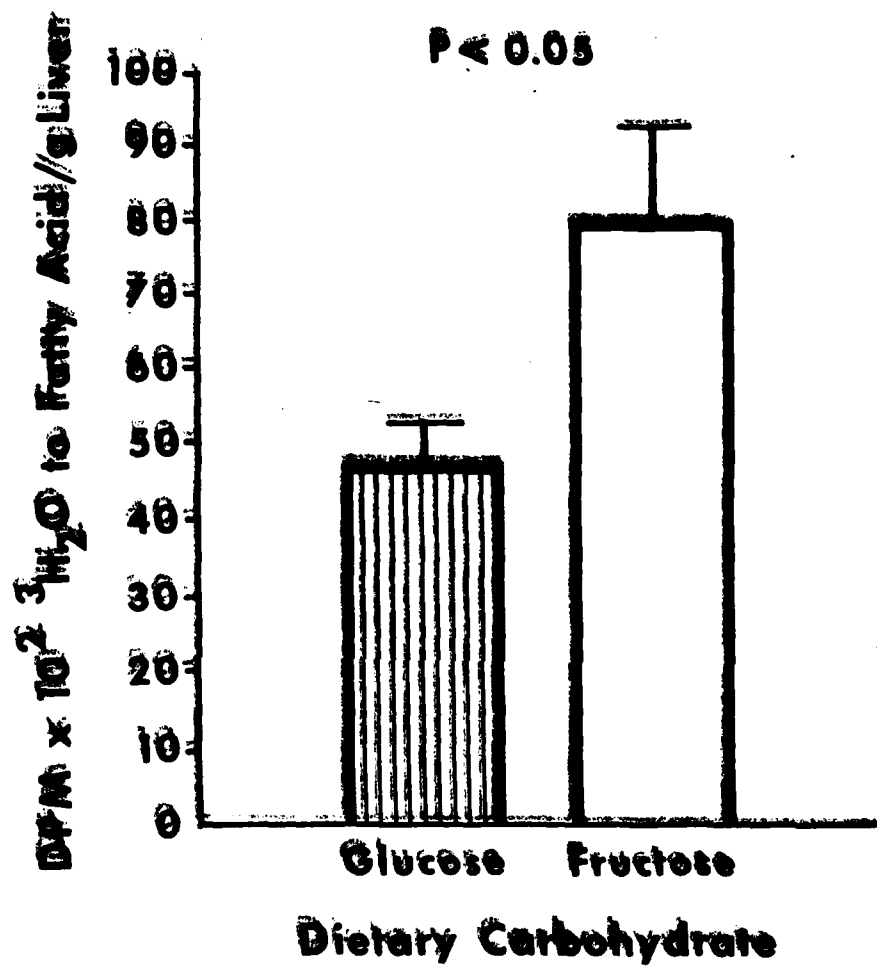


Figure 5

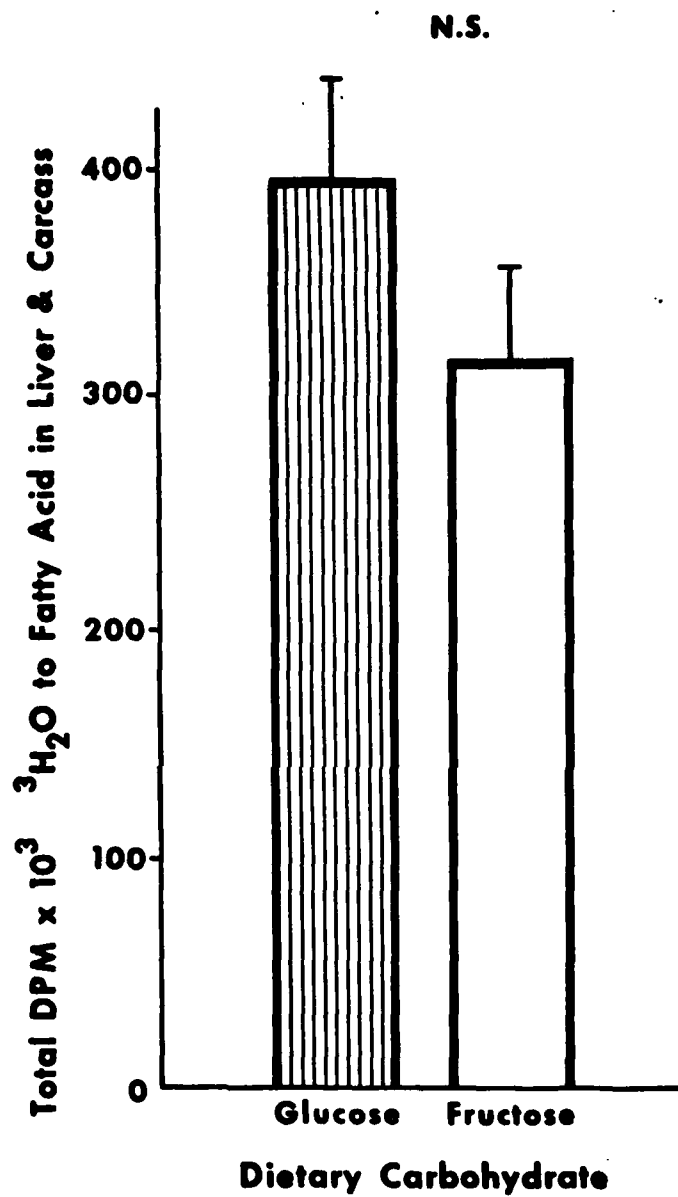


Figure 6

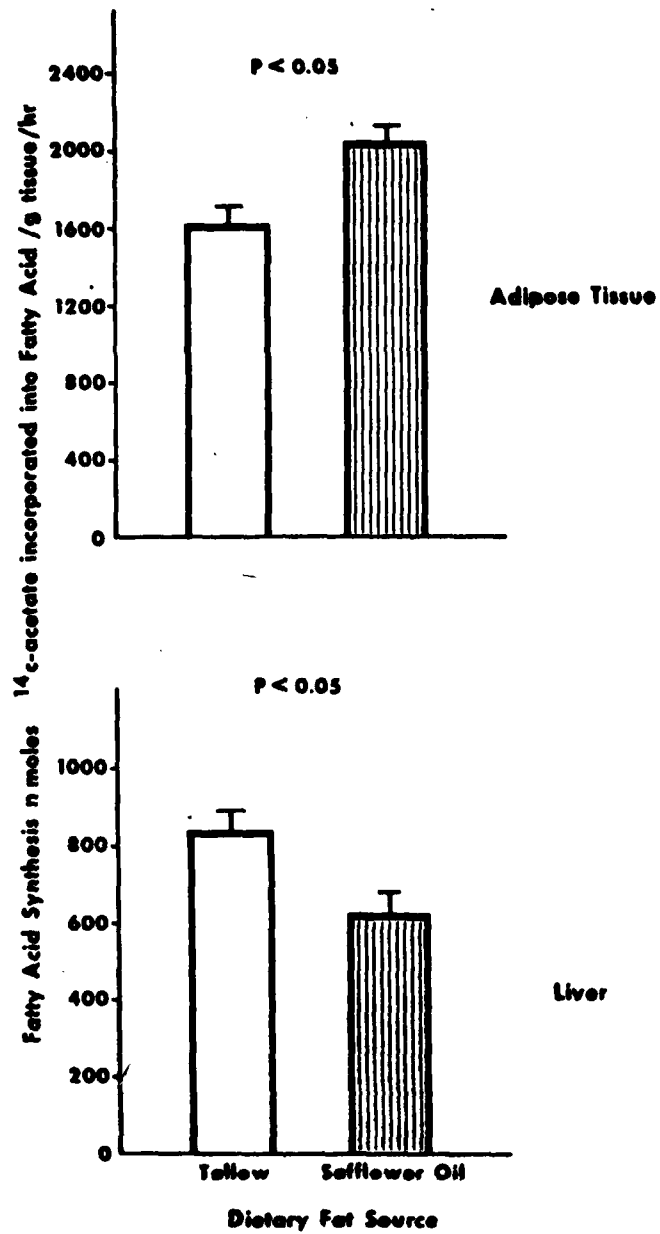


Figure 7

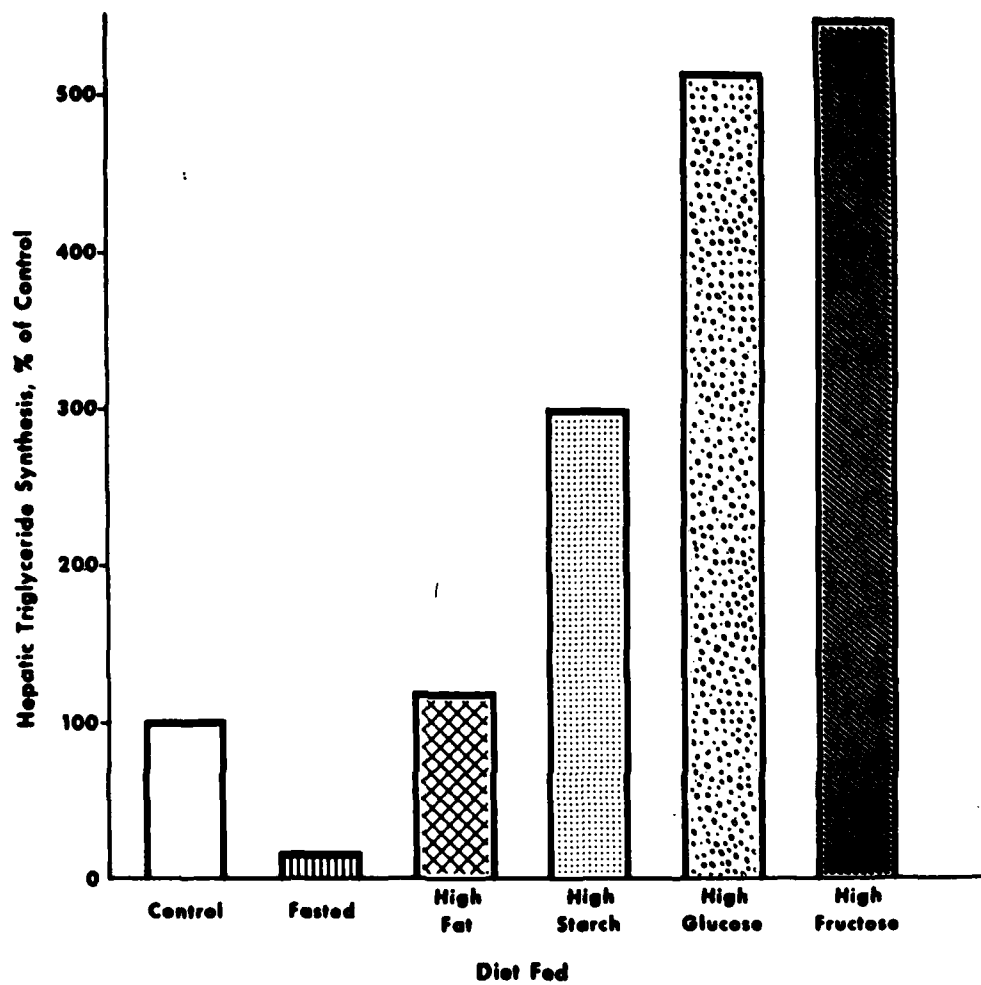


Figure 8

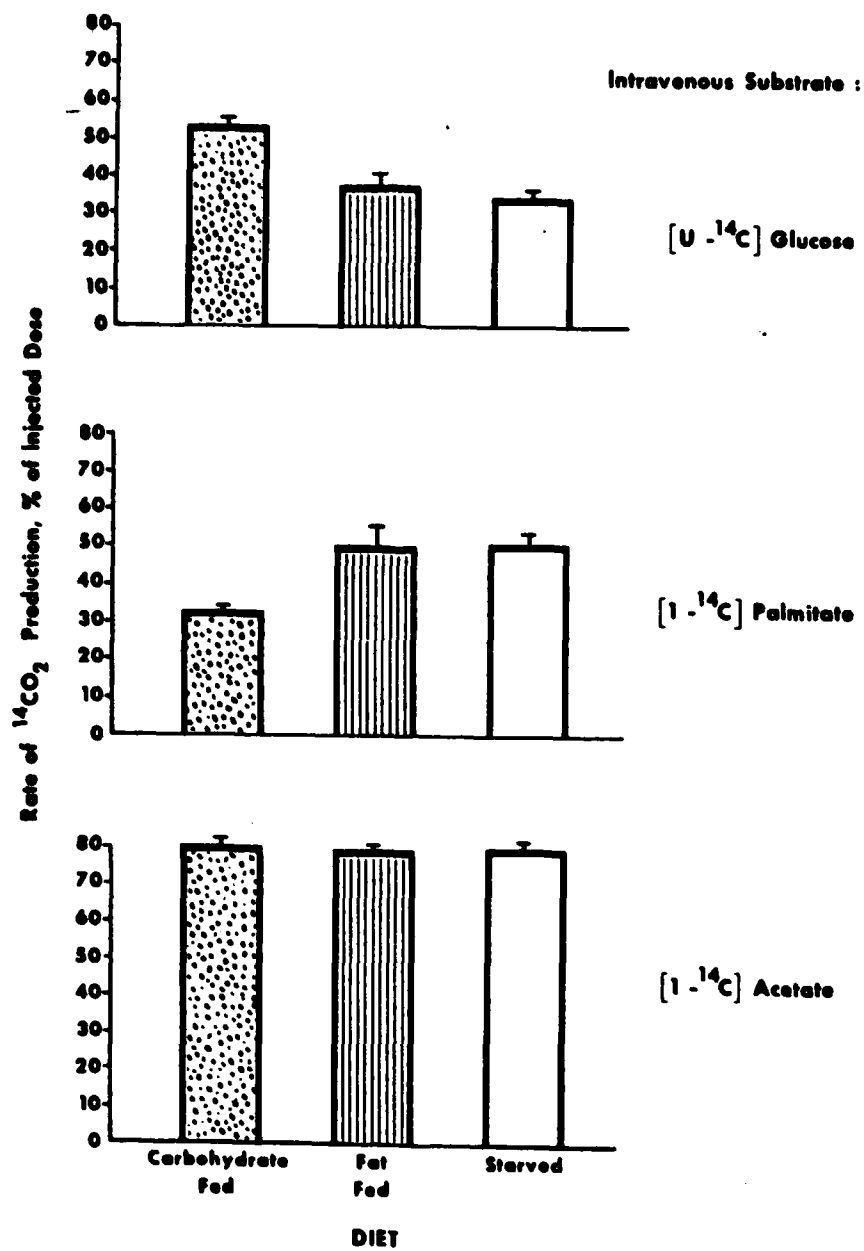


Figure 9

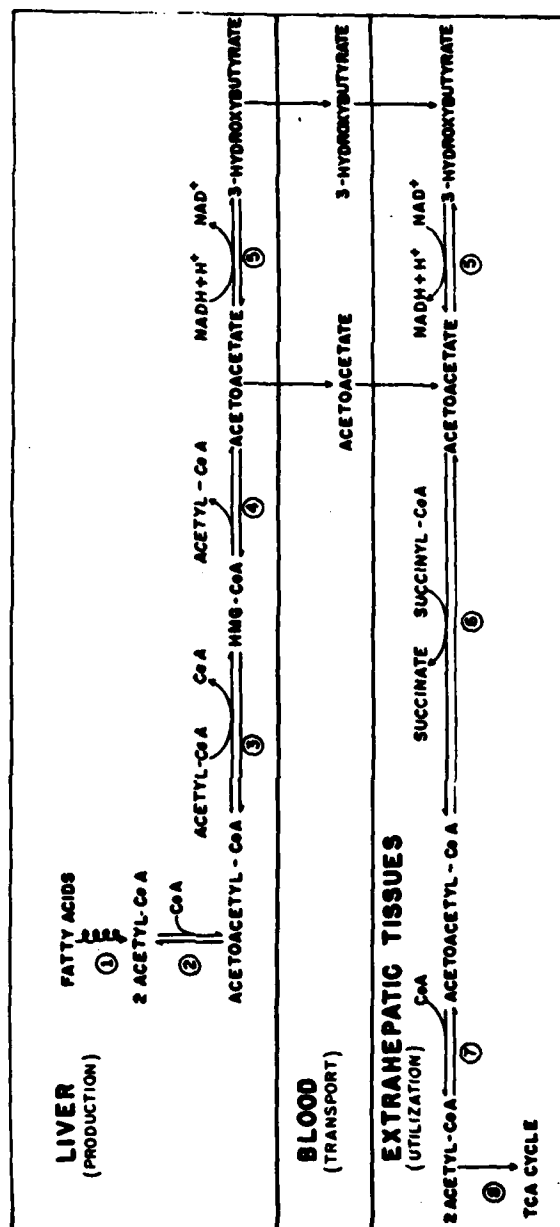


Figure 10

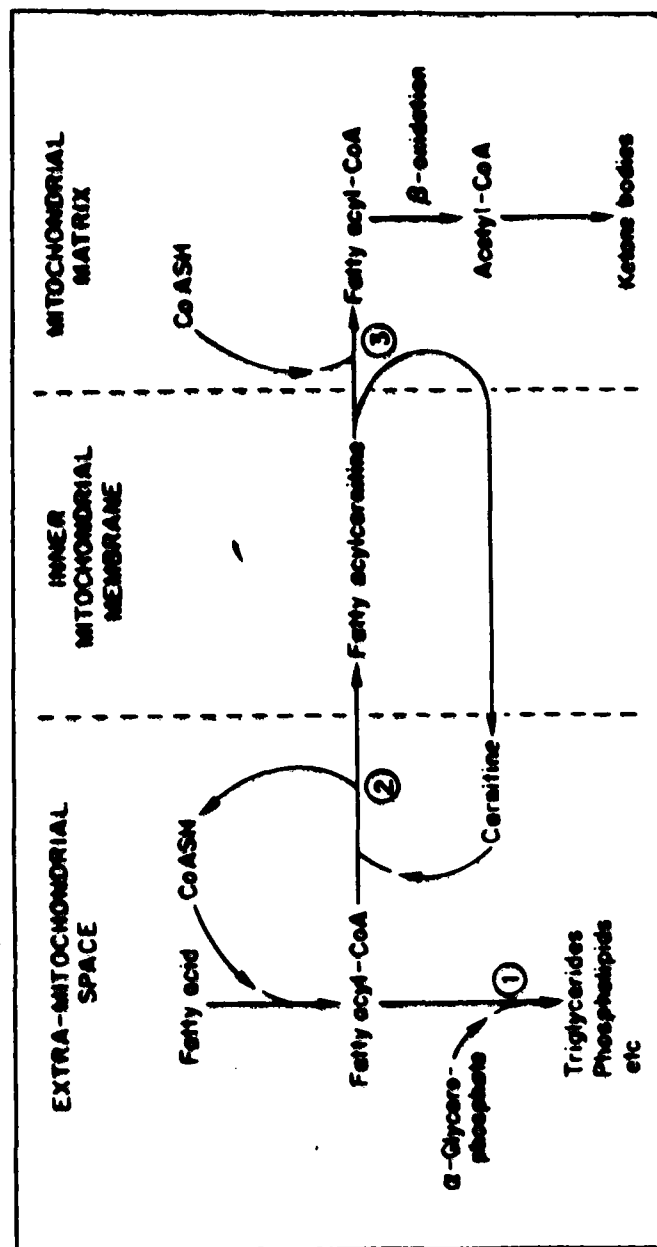


Figure 11

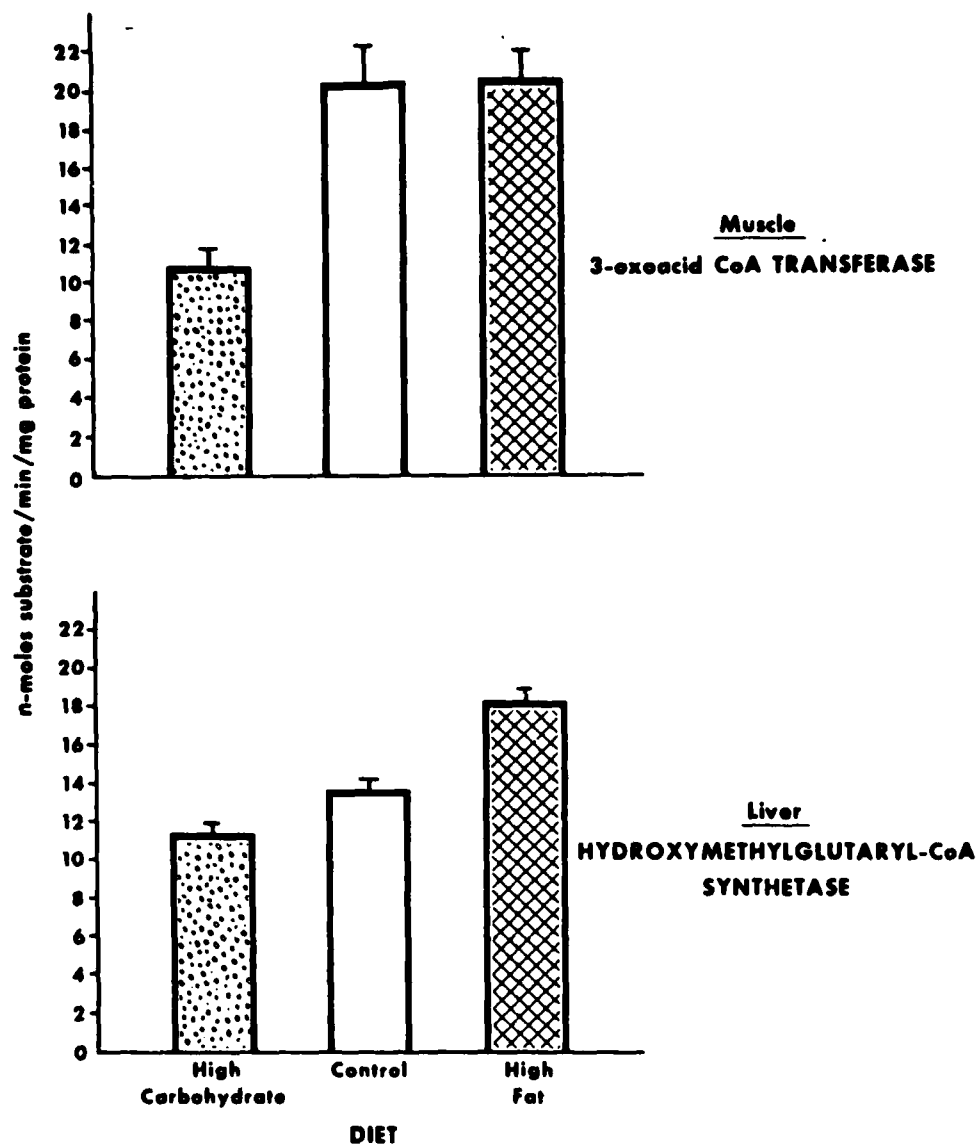


Figure 12

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